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Review Article

Integration of botanicals in contemporary medicine: road blocks, checkpoints and go-ahead signals

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ABSTRACT

The use of botanicals for maintaining good health and preventing diseases is undisputed. The claimed health benefits of natural health products and herbal medicines are based on traditional claims, positive results obtained in preclinical studies and early phase clinical trials that are not backed by safety and efficacy evidences approved by regulatory agencies. Although, the popularity of botanicals is growing, health care practitioners of modern medicine seldom recommend their use because of ill equipped database of their safety and potency. This review discusses problems that preclude botanicals from integrating into the mainstream contemporary therapeutics and cues that provide impetus for their realisation.

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1. Introduction

The use of plants for therapeutic purposes can be traced back to the Neanderthal period and since then their use for remedial purposes has been growing.¹ Animals have also been consuming plants for their healing properties and such serendipitous occurrences have provided leads for identifying plants with medicinal potentials.^{2–5} Many of the drugs in modern therapeutics are natural products or have been derived from them (plants, microbes, marine organisms/plants, insects, animals).^{6–9} Data collected over the years from drug manufacturing community has indicated that about 50% of drugs available in the last several decades had natural

origin and around 27 anticancer drugs including actinomycin D, paclitaxel, vincristine, topotecan, dexamethasone, etoposide, tamoxifen etc. developed during the period 1940–2010, were from natural sources.^{8–10}

The search for medicinally relevant compounds from natural sources is relatively easy because they have a history of use in prevention and/or treatment of diseases. Thus, drug discovery from herbal sources is experience driven and on the contrary, the search of a clinically useful compound ‘de novo’ with no source leads is a ‘shot in the dark’. Drug development from plants is carried out in three elaborate steps namely: pre-drug stage; quasi drug stage and full drug stage.¹¹ Pre-drug stage

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is the first stage of drug development and involves the information driven selection of herbs or plants, based on results obtained in animal studies, experience obtained by their indigenous use and through self-medication. Thus, fruits, vegetables, spices, and traditional medicinal plants are obvious targets for this approach. Once cleared through the pre-drug stage, the plant enters the quasi drug stage which involves the preparation of extracts, screening of phytochemicals, structure and composition elucidation, bioactivity evaluation and identification of possible lead compounds using modern techniques.¹² Once the lead compound is identified, it is structurally modified if needed. It is then evaluated in animal models, in-vitro studies and clinical trials and upon approval; it enters as a marketed drug. All these comprise the full drug stage. Although, modern, scientific and high through put technologies are available for the drug discovery process, however, unless these take care of the ADMET profile (i.e., absorption, distribution, metabolism, excretion, and toxicity) they may not be able to successfully produce a good medicinal product.

The drug development process is growing at an enormous pace and it is undeniable that chemically synthesized drugs have revolutionised the field of medicine. Despite, the well established system of modern conventional medicine, plants still continue to provide benefits for medicinal purposes to about 80% of the world population, largely in developing countries.^{13,14} Over 70–95% of the population in Africa, Asia, Latin America and Middle East use some form of traditional medicine as their first line of treatment.¹⁵ Majority of the hospitals in China have well established units rendering treatment through traditional healing systems.^{16,17} In China, traditional Chinese medicine (TCM) was very widely used for controlling severe acute respiratory distress syndrome and in Africa, traditional herbal medicine was used to alleviate symptoms associated with human immune deficiency virus (HIV) infection.^{18,19} Plant based remedies are the primary form of healthcare amongst the unprivileged sections of populations because of poverty and limited access to modern medicine.

Complementary and alternative medicine (CAM) therapies is divided into two broad categories namely drug based CAM therapies and non-drug based CAM therapies.²⁰ Plants constitute about 80% of the drug based CAM therapies. There has been a change of perception among the general public and adoption of alternative remedies has increased even in the developed nations.^{13,21} Particularly, herbal medicine is drawing attention and has given a boost to the phytopharmaceutical market in international trade. Global giants in pharmaceutical manufacturing have been aggressively investing in herbal medicine.^{17,19} Chinese herbal medicine registered an increase of 20 percent in sales in 2012 from the previous year; reaching to about US\$83 billion.²² The international market for herbal supplements and remedies is expected to reach US\$115 billion by 2020, with Europe being the largest and Asia-Pacific being the fastest growing market.²³ Worldwide, about 35 000 plant species are being used for medicinal purposes.²⁴ The Indian herbal industry uses about 960 plant species and among these about 178 have huge consumption surpassing hundred metric tonnes.²⁵ Among the European countries, Germany and France have the largest sales of herbal medicines.¹⁷ The use of herbal supplements is also very popular in United States of America (USA)

and their eminence for purported health benefits is on a continuous rise.²⁶

Modern medicine targets the disease usually by employing a single agent (monotherapy). Traditional healing systems like ayurveda employ different approaches like medicinal herbs, yoga, dietary control, meditation, prayers etc for restoring balance in the body and alleviation of diseases. Traditional systems of medicine are based on the holistic treatment of the patient which also takes into consideration behavioral, physiological, psychological effects of drugs on the mind-body complex. Ayurvedic medicinal preparations contain combination of medicinal plants, minerals, metals etc. Polyherbal formulations are recommended as they provide synergism of positive effects and antagonism of negative effects and drug associated side effects.^{27,28} The use of multiple herbs in combination with other ingredients and modalities serves well to provide symptomatic relief alongside targeting the disease at the tissue level. The modern chemotherapeutic approaches which are largely 'molecule driven' have taken an edge over traditional healing systems because plant based preparations and other complementary modalities are slow to act and provide relief gradually, in comparison to the drugs used in modern medicine.^{28,29} However, the ill effects emanating from the use of these drugs has provided grounds for renewed interest in traditional therapies.^{30,31}

The increase in adoption of herbal remedies may be ascribed to: a general preference of natural therapies and aversion for other interventions like surgery, allopathic medicines etc; inclination towards self-medication based upon experience; affordable cost of herbal medicines and ease of availability; side effects associated with conventional medicines (especially in cases of chronic problems) and growing promotion of herbal medicines.^{13,32} Herbal remedies are generally used and/or recommended for maintaining good health, alleviation of chronic problems and rarely for acute and/or life-threatening problems.^{33,34} People begin using alternative forms of treatment, including herbal medicine when conventional medicine is ineffective or for pain palliation in case of long standing problems like cancer, arthritis etc.¹⁷ The use of natural dietary supplements among the general population is also very popular in an attempt to prevent cancer.^{35,36} The use of dietary supplements (containing natural products) among cancer patients in USA has become very popular and many patients begin using new dietary supplements with natural ingredients after being given a cancer diagnosis.³⁷ Botanicals when sold commercially are often referred to as 'natural health products (NHPs) or herbal medicinal products (HMPs)'. They are available as single isolated/enriched compounds or as complex mixtures of several biologically active compounds and they may be obtained from single herb or combination of herbs (polyherb formulations). They are prepared in a variety of ways and can be taken in the form of decoction, tinctures, essential oils, teas, syrup, ointments, salves, and tablets/capsules that contain powdered form of the whole plant/plant part or dried extract.¹⁷

Although, the adoption of herbal medicine/botanicals in preventing and/or curing diseases through self-medication instigated by promotion in popular media has seen a surge,³⁸ however, its acceptance among health care practitioners is not very encouraging.^{39–41} Strange as it may appear, but many

professional health practitioners admitted to having little knowledge regarding herb supplements, which discourages their prospective clinical trials and use. It was revealed in a survey that oncologists did not have enough knowledge about the use of herbs and dietary supplements and did not receive any training in this regard. Due to lack of concrete evidence and scientifically robust studies evaluating their potential risks and benefits, oncologists find it challenging to give advice to patients regarding their use, probable positive or negative impact along with the use of other treatment modalities like radiotherapy, chemotherapy, hormonal therapy, immunotherapy etc.^{37,42}

Although, many botanicals are in the pipeline of clinical trials however, they have met with little success because of the study limitations.⁴³ Therefore, health care practitioners seldom recommend/prescribe their use in ailments. The widespread promotion of the natural products/dietary supplements claiming their health benefits through television, internet etc is one of the major sources through which the consumers gain knowledge about these products. These claims are usually not backed by any regulatory authority and generally are based on positive results obtained in pre-clinical investigations in animal models, cell lines and/or small early phase clinical trials. The use of these products bereft of any safety and efficacy studies is likely to have some detrimental effects. For instance, in USA, for cancer, several clinical trials have been conceived and initiated but Food and Drug Administration (FDA) has not approved any phytoproduct in cancer therapy. A lot of natural dietary supplements have undergone phase 2 trials; however, majority failed to enter the follow up phase 3 trials.^{37,43} Plant extracts encounter steep failure rates in clinical trials which is in sharp contrast to the enormous benefits they exhibit in pre-clinical studies.³⁷ Thus, they fail to obtain the regulatory approval as potential treatment options.

This review discusses various problems encountered with botanicals/phytomedicine and its possible integration with the contemporary medicine (Fig. 1). Some of the impediments are inherent to this healing system and there are other problems which fall in the ambit of regulations and procedures. Even though, there has been a paradigm shift in the mindset of people regarding the use of natural products, however unless backed by their safety and efficacy proofs they are unlikely to be recommended as popularly as the contemporary form of medicine.

2. Problems that keep botanicals away from being included in the mainstream alternatives for health promotion and disease management

Scientifically sound and robust procedures and guidelines have been laid down for assessing safety, efficacy, pharmacokinetics, quality, good manufacturing practices (GMP), post marketing surveillance etc of conventional putative drugs. However, such rigorous procedures are lacking for herbal products. In addition, clinical trials with herbal products are associated with poor design and reporting. This is surprising considering the fact that this form of medicine enjoys such tremendous popularity amongst the people of both developed

and developing nations and of all cultures and religion. All these reasons account for the hazy reputation of botanicals.

2.1. Challenges of clinical trials: impediments in trial designing, poor design of trials and their reporting, economically unviable trials

Carrying out of randomised, placebo-controlled trials is essential in the evaluation of any drug for health benefits or disease mitigation.³⁷ Usually herbal medicines have a peculiar color, taste and smell which make it difficult to carry out placebo-controlled trials.^{44,45} In addition, the decision to choose an 'active reference medicine/comparator' as a herbal product or one that from modern medicine is an area of concern. Quite literally, it is very difficult and impractical to have active and control groups with similar organoleptic features when using herbal products.⁴⁶ The differences in the type of formulations used, although containing the same ingredients yield different results owing to the varying bioavailability of the active constituents.⁴⁷ Although, the inclusion and exclusion criteria for enrolling patients in clinical trials with HMPs could be based either on modern or traditional practice, however, confounding situations could arise if the disease criteria vary in both the systems.⁴⁶ The inclusion and exclusion criteria for trials with herbal medicine are challenged by the non-uniformity in medical systems across countries.⁴⁸ Overlooking such issues can allow for faulty interpretations and conclusions. For instance, the criteria for patient selection by American researchers for testing the potential of a herb on heart failure would be based on the disease features recognised by the New York Heart Association, which drastically differs from the 'ying and yang' perspective of disease development by the practitioners of TCM.¹⁹

Ayurveda (Indian form of traditional herbal medicine) treats patients on the basis of 'prakriti' or the 'psychosomatic' constitution. This is an individualistic thing and ayurveda recommends compounding/mixing of herbs, dosage and duration for an individual. Therefore, the effect of one particular treatment regimen of an ayurvedic remedy would be inappropriate to generalise to a subject population with varying psychosomatic constitution in clinical studies.^{49,50} Such generalisation could also be difficult to apply to other traditional forms of medicine like TCM which lays stress on personalised medicine.⁵¹

Clinical evaluation of herbal drugs has been found to have shortcomings in trial design, improper execution and weak data analysis.⁵² Inappropriate number of patients in trials, improper randomisation and selection bias has been observed in previous clinical trials with herbal medicines.^{53,54} Enrolling fewer participants in the trial make it difficult to reach to a statistically significant conclusion. Many a times, doubts and objections have been raised on the methodology and inferences drawn from clinical trials of herbal treatments. In addition, reports on herbal drugs are incomplete with respect to the recommendations of Consolidated Standards of Reporting Trials (CONSORT) guidelines,⁵⁵⁻⁵⁷ explaining the elusiveness and contradiction in their safety and efficacy reviews.⁵⁸⁻⁶⁰ Considering these limitations, Cochrane reviews had concluded that with herbal drugs no well-designed trial has been conducted and that there is not enough supporting

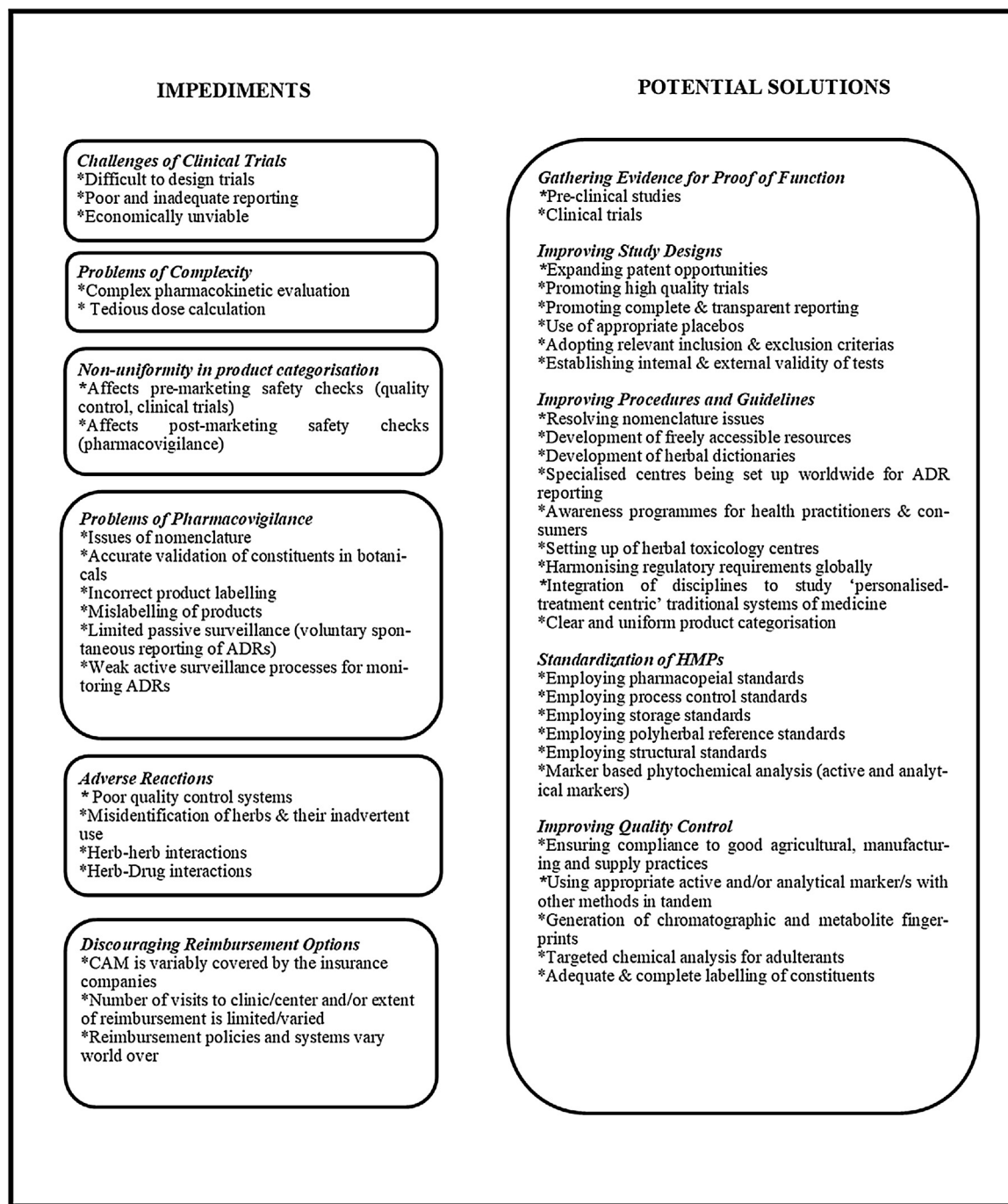


Fig. 1 – Inclusion of botanicals in contemporary medicine: obstacles encountered and potential solutions (a brief summary)

evidence for their safety and effectiveness for the proposed clinical condition.^{61–67} Poor quality of trials and their reporting give way to under or overestimation of the treatment effects which are bound to have undesired effects. Also, the conclusions made regarding the efficacy are surrounded by doubts linked to poor quality of reporting and poor design and conduct of trials.⁶⁸ Very few clinical trials involving traditional herbal medicines in Africa and China have been reported to be of adequate quality and problems have been recognised with regard to number of patients recruited, placebo preparation etc.^{69–71}

Repetitive and large scale clinical trials are complicated, time consuming and expensive procedures. Usually, the compound/drug molecule undergoing clinical trials is patented by the pharmaceutical company and these are then sold at a premium providing opportunities for the manufacturers to gain profits. Usually, manufactures of food products, herbal products etc are not given patent protection and therefore face price competition. Limited profits incurred dissuade them from paying the hefty costs involved in large phase 3 trials.³⁷ In USA, since FDA approval is not mandatory for selling dietary supplements containing herbal ingredients, therefore,

manufacturers avoid going through randomised, placebo-controlled phase 3 trials and continue promoting their products based upon the positive results obtained in phase 2 trials. Due to the fact that plants cannot be patented, therefore drug manufacturers see fewer opportunities for huge profit making. In USA, approximately \$5.5 billion to 5.9 billion and 15 years is the amount of money and time spent in bringing a new drug to the market.^{72,73} Without huge profits in sight, very few companies are willing to invest in satisfying FDA requirements.

2.2. Problems of complexity: difficult pharmacokinetic evaluation and dosage calculation

Pharmacokinetic studies are difficult to carry out on polychemical natural products.⁷⁴ This is because many a times, the active ingredient/active principle is not known, and also the presence of several different active components make the pharmacokinetic evaluation difficult and complex.^{75–77} The problems of pharmacokinetic profiling in phase I of drug development are further compounded in cases when polyherbal formulations are used. This requires standardisation of several active compounds and their estimation in the body fluids.⁷⁸ Pharmacokinetic evaluation becomes very elaborate when patients simultaneously seek treatment from traditional and contemporary medicine systems.

Pharmacokinetic herb–drug interactions are mediated by modulations in cytochrome P450s (CYPs) and drug transporters (P-glycoprotein).⁷⁹ CYPs are primarily involved in drug metabolism and are abundantly present in liver and small intestine. CYP3A4, one of the isoform of CYPs is an important drug metabolising enzyme (DMEs) that is involved in the herb–drug interactions.⁸⁰ It is responsible for oxidising about 60% of drugs to less active or readily excretable metabolites and its level of activity determines the bioavailability of the drug. Any alteration in the activity of CYP3A4 gets reflected in the bioavailability of drugs that are oxidised by this CYP. For instance, it has been observed that grapefruit reduces enteric CYP3A4 activity, thereby elevating the levels of some drugs to toxic levels.⁸¹ On the contrary, St. John's wort, which is used in the treatment of depression increases CYP3A4 activity and P-glycoprotein, consequentially leading to diminished clinical response of drugs like cyclosporine and indinivir.^{82,83} Since, the drug entities of both the systems are metabolised by the same monooxygenase system (DMEs) in the body, therefore pharmacokinetic interactions are inevitable. Further, polymorphism in DMEs is likely to have its own influence on the way individuals respond to herbal medicines.⁸⁴

Conventional medicines are carefully studied for their dose effect response and accordingly safest dose is calculated taking into consideration body weight, drug interactions etc and possibly minimising the scope for negative effects.^{44,85,86} Dose calculation is a tricky area to resolve in herbal medicine due to several reasons. Very often the active ingredient/s and the quantity is unknown in the herb and its raw material by which the herbal medicine is prepared. More so, very rarely it is known as to how the levels of the active constituents vary with the kind of processing the herb undergoes for preparation of drug.⁸⁷ In vitro and pre-clinical studies involve prolonged exposure to high concentrations of the phytoproduct. This may be difficult to imitate in humans because of limited oral

bioavailability, known and unknown adverse effects and drug interactions rendering such treatment regimens unsuitable.⁸⁸ Because of the inadequate studies determining the interactions of herbal medicines with the conventional medicines there is a likelihood of adverse drug reactions (ADRs). Not only this, insufficient information is available regarding the dose dependent effects and possible side effects of the same on consumption of higher doses. For instance, although herbal remedies are effective in controlling progression of liver diseases, however some of the compounds present in these medicines can have deleterious effects. Thus, this necessitates careful dose escalation and efficacy testing which involves complex pharmacokinetic and dose calculation studies.⁸⁹ Traditional forms of medicine used in China, Japan, Korea, India etc are mainly used in the form of decoction which involves boiling of the plant parts to extract/enrich the compounds of interest. Decoctions suffer from disadvantages like dosage quantification, composition stability, quality control etc. Discrepancies in the reported dosage and treatment duration of herbal remedies; poor standardisation and lack of quality control of herbal preparations, presence of several active compounds are some issues that make the dose calculation tedious.⁷⁷

2.3. Product categorization affects safety assessments: pre-marketing and post-marketing safety checks

Herbal products are classified and regulated depending upon countries/jurisdiction.⁹⁰ The regulatory requirements for products labelled as 'food' are less stringent than those labelled as 'drugs' or 'medicinal products'. This categorisation varies between countries and sometimes even within the countries.^{91,92} Product categorisation can be a difficult task, sometimes vague, presenting challenges to the regulatory authorities. The claims made regarding the products enlists them either into food or drugs i.e. products which claim no health or medicinal benefits (treat or prevent diseases) are labelled as 'food'. For instance, if products containing garlic are claimed to exhibit health benefits then they are regulated as drugs, else are sold as food.⁶⁸

In USA, herbal products are classified as dietary supplements or special foods and since they are not considered as drugs, therefore they can be sold without clinical trials and do not require pharmacovigilance reporting.⁹³ Thus, FDA does not subject them to the same strict and thorough intensity checks of proof and safety. They are regulated under the Dietary Supplement Health and Education Act, which allows their use without having them to clear the strict quality control tests of Drugs and Cosmetics Acts (1994). FDA only reviews these products and does not approve them. Accordingly, it is not mandatory for manufacturers to test them in clinical trials before marketing them, thus allowing for any untoward effects that could occur with their use. FDA can disallow a company from making a supplement after it has been shown to cause adverse effects.⁹⁴ Several such cases have been reported where herbal products have been recalled after they were found containing banned substances or substances unfit for consumption like prescription drugs etc. FDA banned the sale of ephedra following reports of ephedra-related toxicity and deaths.⁹⁵ This is in striking contrast to the regulations for

prescription and non-prescription drugs which are required to be proven safe before selling. Pharmacovigilance reporting (ADR reporting) is also not mandatory for manufacturers of herbal dietary supplements.⁹⁶ In the European Union (EU), herbal products are classified either as herbal medicines or as food supplements depending upon the claims made. Herbal medicines in EU are required to satisfy safety and quality standards but food supplements are not required to do so. Complexity arises in cases when the same herb or mixture of herbs is being supplied as herbal medicine and dietary supplement. Thus, labelling a herbal product as drug or food has implications in its pre-marketing (quality control, clinical trials) and post marketing safety checks (pharmacovigilance).⁹⁶ In China, natural products are considered as medicinal products and therefore are subjected to similar level of regulatory control as for the conventional medicines. The regulatory guidelines for countries like Canada, Singapore, Australia etc vary and regulate the products accordingly.⁶⁸ This non-uniformity in product categorisation not only affects their pre-market and post-market control, their safety and efficacy, but also poses challenges in trans-national movement of products.

2.4. Challenges of pharmacovigilance: complexity of nomenclature and consumer related issues

Since herbal drugs available worldwide come from China, India, Brazil, Africa, several countries of Europe, South America etc, therefore there are problems that come up due to diversity. This brings to the forefront questions such as what should be the appropriate naming system (Latin, pharmaceutical, generic, herbal drug name) and accurate validation of the constituent herbs. Plants/herbs are generally known via their Latin scientific name, vernacular name, pharmaceutical name or pharmacopoeial name or specific herbal drug names (as used in TCM or Indian herbal medicine). Sometimes, different herbal ingredients are known by a single name allowing for misidentification and inadvertent use of herbal products leading to undesired effects.⁶⁸ The roots of *Aristolochia fangchi*, *Stephania tetrandra* and *Cocculus trilobus* are commonly known as Fang ji. *A. fangchi* (Guang Fang Ji) was mistakenly consumed instead of *S. tetrandra* (Han Fang Ji) for its weight loss benefits and consumers reported severe renal problems. Upon careful analysis it was found that inadvertent consumption of aristolochic acid containing *A. fangchi* (Guang Fang Ji) products was responsible for such adverse effects.^{97–99} This was followed by a ban of aristolochic acid containing herbal products in EU, USA and Australia. However, misidentification of herbs due to confusion/similarity in common names continued the production and consumption of aristolochic acid containing herbal products.^{100–104} Product labelling of drugs may use one or more of these naming systems and at times the drugs are even sold without any labels. The non-uniformity in describing herbal constituents makes ADR and analysis confounding, sometimes wrongly implicating a herb to the observed negative outcomes. Although, common names are frequently used in USA and EU for the purpose of reference, however, EU regulatory authorities recommend the use of Latin scientific names.⁹⁶ Reporting of herbal ADRs is of use only if the reporter is aware of what herb/product was used. This requires

correct identification of the plant/herb by the user. Inadequate or inappropriate use of names can cause confusion. For instance, ADRs reporting by referring to the use of ‘ginseng’ could point out to a variety of plants, their species or even unrelated plants. ‘Ginseng’ may refer to *Panax ginseng* C.A. Mey or *Panax quinquefolius* (Burk.) F.H. Chen or other plants that are also referred to as ginseng such as *Eleutherococcus senticosus* (Rupr. & Maxim) Maxim (Siberian ginseng) or the unrelated *Withania somnifera* (L.) Dunal (Indian Ginseng).⁹⁶

It is a general perception among consumers that herbal products have low risk so much so that anything natural is synonymous with being safe. Any untoward effects observed upon their consumption are generally not accepted and thus ‘cause–effect’ is not acknowledged in this case. Because of this unawareness or paucity of information, users very often defer the notion that their adoption of herbal remedy may be causing the observed unfavourable effects. Thus, their prolonged use of herbal products could aggravate the problem. This is particularly prevalent in the developing countries where use of traditional herbal medicine is very popular and the system of reporting ADRs is not well constituted. Surveys conducted in developed nations like USA, Canada, United Kingdom (UK), Australia have indicated that in these nations ‘passive surveillance’ (voluntary spontaneous reporting) is the prime source of gathering information about adverse effects emanating from the use of medicinal products including NHPs.¹⁰⁵ Although, passive surveillance has the advantage of revealing adverse effects in ‘real’ situations (large population/wide consumer base) however, it has its limitations which can be understood from the fact that since this system depends upon voluntary reporting by the practitioners and/or patients, less than 1% of adverse effects are reported.¹⁰⁶ More so, patients and health care practitioners are less likely to report adverse effects associated with the use of NHPs than with the conventional over the counter medications. It has also been observed that physicians do not routinely inquire patients about use of NHPs.^{106–111} Collectively, all these factors contribute to the inadequacy of the passive surveillance to identify NHP associated harms. Active surveillance which involves keeping track of adverse events using a carefully chalked out pre-organized process are well established for conventional prescription medicines but its application to NHPs is limited till date.^{112–114} For reasons known and unknown, patients do not divulge to their clinicians about their use of herbal medicines.³⁸ The consumers are unaware of the importance of reporting the use of herbal products or the adverse effects that may have emanated from their use.¹¹⁵ In case of ill effects, patients and health care professionals can report such events, but such reporting is not mandatory.⁹⁴ This leads to underreporting of their adverse effects which contributes to their poor database of toxicity and drug interactions.

2.5. Adverse reactions: an outcome of poor quality control, herb–drug/herb–herb interactions

Several reports are available regarding the undesirable effects of natural products, sometimes with very dire consequences. Such observations have been reported amongst the users of both developed and developing nations. The adverse effects emanating from the use of herbal products can be attributed

to the toxic effects of the inherent constituents or the adulterants/contaminants that are present in the preparation and also herb–drug/herb–herb interactions. Owing to the poor quality control standards and improper regulation of purity and potency, herbal products fall short in comparison to the conventional drugs. Poor quality control systems and lack of stringent monitoring systems lead to the contamination/adulterations of herbal preparations.

Herbs obtained from polluted sites (areas with soil, water or air pollution due industrial emissions) or poor farming practices lead to the production of low quality products unfit for human consumption.^{116,117} Herbal preparations although prepared from same herbs each time may vary from batch to batch because the phytochemical content could fluctuate depending upon the harvesting time of the plant, climatic conditions, geographical locations, harvesting methods and environmental conditions could affect the presence of certain elements (like heavy metals) depending upon the conditions of water, soil and air in that region.^{32,86,118} Inappropriate storage conditions can affect the quality of herbal products if they get subjected to fungal or bacterial contamination and also excessive drying can lead to loss of thermo-labile bioactive constituents.^{84,86} Variations may also arise in preparations such as extracts, decoctions etc between batches and amongst manufacturers because of the variation in solvents, temperature, extraction time etc.¹⁷ The variability in the preparation of the herbal products has implications in the health benefits observed.^{67,86} The likely presence of allergens, pollens, toxins (aflatoxin, mycotoxins brevetoxin B, yessotoxins, pectenotoxins, digoxin, sikimitoxin),^{119–122} microbes (*Escherichia coli*, *Salmonella*, *Listeria monocytogenes*) and heavy toxic metals (mercury, cadmium, lead, arsenic)^{123–128} could be contributing to the observed adverse effects. Several cases of deliberate addition of prescription drugs/other pharmaceutical products (aminopyrine, phenylbutazone, phenacetin, dexamethasone, indometacin, diazepam, hydrocortisone, fluocinolone acetonide, diclofenac, mefenamic acid, clobetasol propionate, phenytoin, methylsalicylate, prednisolone, indomethacin and glibenclamide etc)^{123,124,129} in herbal products have come to light. Cadmium, arsenic and lead have been detected in the herbal products with levels exceeding the maximum permissible limits allowed by World Health Organisation (WHO).^{130,131} Inadvertent adulteration and substitution of herbal drugs with incorrect plants/herbs due to confusion in vernacular names, similarity in color and morphology etc is one of the reasons for herbal products exhibiting undesired effects and being unfit for consumption.^{132,133}

Botanicals contain many pharmacologically active compounds that exhibit biological effects in synergism or antagonism. The presence of multiple compounds increases the likelihood of interactions and it is considered that herb–drug interactions could be more pronounced than drug–drug interactions. These interactions could either serve to enhance or diminish the pharmacological or toxicological effects. Such interactions are mediated due to the pharmacokinetic interference of one xenobiotic on another xenobiotic, including metabolism, elimination, absorption etc. All these events would modulate the dose response observed and therapeutic or toxic effects.¹²⁸ Although, interactions could be positive, negative or neutral¹³⁴; however, they could

be of concern if they act to cause damage. Many a times, there is mislabelling/incomplete information provided on the labels which increases the chances of herb–drug/herb–herb interactions etc.^{135–137}

Consumption of poor quality and adulterated products has led to many unfavourable effects ranging from mild to moderate to severe; such as allergic reactions, respiratory complaints, pain, nausea, fatigue, gastrointestinal upset, mood disturbances, muscle weakness, vomiting, confusion, lethargy, seizures, sensory disturbances, compression fractures, leucopenia, convulsions, persistent hypoglycaemia, Cushing's syndrome, burns, dermatitis, meningitis, multi-organ failure, arsenic, lead or mercury poisoning, malignancies, hepatic and renal toxicity, cerebral edema, coma, intracerebral haemorrhage, and even death.^{13,129,138}

2.6. Discouraging reimbursement options

Worldwide, the use of CAM is increasing and has been a major contributor to non-reimbursed medical or health expenditure. Insurance companies refuse to cover CAM because they do not completely believe the claims made by the proponents of CAM.¹³⁹ The decision makers in the insurance sector reason out that in the current scenario of escalating healthcare costs, and the constant emergence of new medical technologies and drugs has made them wary of expanding the health care coverage options. They are of the opinion that coverage should only be provided for health facilities that are backed by a robust body of evidence for their safety and effectiveness. Moreover, the lack of information on the use, cost and overall cost-effectiveness of CAM makes it difficult for the insurance companies to respond to the consumer needs and hinders their ability to plan and execute policies related to CAM reimbursement.¹³⁹ In USA, the private insurance companies provide cover to varying degrees for the medical expenses incurred from the accepted standard of care modalities and reimbursement is usually not available for CAM and therefore must be paid of pocket by the consumers.¹⁴⁰ Although, CAM is very popularly used in UK, however it is not covered by the healthcare system.¹⁴¹ Since, the introduction of Statutory Health Insurance Modernization Act in 2004, the sale of herbal medicines has dropped in Germany because of the exclusion of phytotherapeutics from reimbursement.¹⁴² In USA, Medicare and Medicaid plans selectively provide cover for chiropractic care, massage and acupuncture and have excluded other forms of CAM including phytomedicine from the reimbursement plans.^{143–145} Private insurance companies have begun to include some forms of CAM however pre-authorization, network restrictions, deductibles, co-payments may be more than those laid out for conventional treatment options. Additionally, the number of visits to the clinic/centre and the extent of reimbursement may vary and be limited. In EU, the reimbursement systems and policies differ between the countries and in many countries, CAM is not included in the national health supervision system.¹⁴⁶ This implies that patients seeking CAM treatment outside of their home country may not be able to receive reimbursement because the CAM reimbursement policies may differ between their country of affiliation and the country of treatment.

Table 1 – Medicinal effects exhibited by some plants

Plant	Beneficial effects observed	Reported literature
<i>Azadirachta indica</i> (Neem)	Anti-cancer, anti-toxic, anti-viral	148–154,156,175
<i>Lycopersicon esculentum</i> (Tomato)	Anticancer, anti-toxic	155,157
<i>Aloe barbadensis</i> (Aloe vera)	Radioprotective	158,159
<i>Withania somnifera</i> (Ashwagandha)	Anti-cancer, anti-toxic	160,161–164
<i>Ginkgo biloba</i> (Ginkgo)	Neuroprotective, nootropic	165–168
<i>Alpinia galangal</i> (Greater galangal)	Fertility	121,171
<i>Punica granatum</i> (Pomegranate)	Fertility	121,171
<i>Viscum album</i> (Mistletoe)	Immunity booster in cancer patients, mitigates chemotherapy associated side effects	172
<i>Thymus vulgaris</i> (Thyme)	Cold, cough, bronchitis, respiratory tract ailments	173
<i>Pimpinella anisum</i> (Aniseed)	Cold, cough, bronchitis, respiratory tract ailments	173
<i>Althea officinalis</i> (Marshmallow)	Cold, cough, bronchitis, respiratory tract ailments	173
<i>Serenoa repens</i> (Saw palmetto)	Urinary tract ailments	174
<i>Artemisia annua</i> (Sweet wormwood)	Anti-arthritis, anti-inflammatory	176

3. Growing prospects of botanicals

Although there are numerous deterrents in the field of phyto-medicine, however, efforts are being concerted globally to gain maximum benefits from the healing powers of plants. Despite the apprehended hiccups, researchers worldwide have been carrying out pre-clinical studies and clinical trials with botanicals. Agencies like National Institute of Health (clinicaltrials.gov), USA; European Medicines Agency [EMA] (clinicaltrialsregister.eu), London; Indian Council of Medical Research (ctri.nic.in), India; National Health and Medical Research Council, Australia (anzctr.org.au) etc in assistance with several government and private institutes undertake clinical trials and maintain their database. Typical pharmacopoeial standards are difficult to apply to herbal medicines and thus require broader and flexible approach in addressing the problem of standardization.^{85,147} Systems and procedures are being developed and revised to improve quality control, safety and efficacy testing and pharmacovigilance.

3.1. Gathering scientific evidence for their proof of function: pre-clinical and clinical studies

Plants are being continually explored for their medicinal properties in various animal, in-vitro models of diseases and their suitability is also assessed in clinical studies (Table 1). The underlying mechanisms behind the observed beneficial effects are also being studied extensively. Several studies from our laboratory and those of others have demonstrated the anticancer effects of *Azadirachta indica* (Neem) extract against cancer of various sites in mice.^{148–154} Lycopene enriched tomato extract has proved beneficial against liver cancer in mice.¹⁵⁵ The anticancer activity has been ascribed to their ability to modulate key signalling pathways like cell proliferation, apoptosis, carcinogen biotransformation, DNA repair, immunomodulation etc. Neem and tomato extracts have been effective in ameliorating doxorubicin induced cardiac¹⁵⁶ and renal¹⁵⁷ toxicity in mice. Administration of *Aloe vera* extract provided protection against radiation induced testicular damage in mice by its ability to scavenge free radicals and strengthen the cellular anti-oxidant defense system.^{158,159} *Withania somnifera* has the ability to mitigate arsenic induced

toxicity in rats.¹⁶⁰ Several researchers have investigated the anticancer effects of *Withania somnifera* against skin, prostate, colon, leukemia etc in animal models and cell lines.^{161–164} Extracts of *Ginkgo biloba* has neuroprotective effects as revealed by its ability to prevent ischemic brain damage in mice¹⁶⁵ and trimethyltin neuronal toxicity.¹⁶⁶ *Ginkgo biloba* has also exhibited nootropic effects.^{167,168} Myriad number of phytochemicals present in fruits, vegetables, herbs etc have been demonstrated to have a wide range of biological activities that are responsible for their medicinal properties.^{169,170}

In a randomised control, double blinded trial, plant extracts of *Alpinia galanga* (greater galangal) and *Punica granatum* (pomegranate) were assessed for their effects in improving semen quality in males (NCT01357044; clinicaltrials.gov) and the study findings suggested that subfertile men can gain an improved amount of motile ejaculated sperms by taking tablets containing preparations of pomegranate fruit extract and rhizome of greater galangal.^{121,171} A gel prepared with *Solanum undatum* plant extract is being tested for its safety and efficacy in patients of actinic keratosis (NCT01516515; NCT02559934), vulvar pre-cancerous lesions and cutaneous condyloma (NCT01676792). Mistletoe plant extract has been assessed for its ability to improve immune function in stage IV lung cancer patients receiving conventional chemotherapy (NCT00079794). Its use as a complementary treatment led to chemotherapy dose reductions, fewer hospitalisations and reduction in non-haematological side-effects.¹⁷² Plant extracts have been tested for their ability to provide relief against nasopharyngitis and upper respiratory tract infection (EudraCT Number: 2005-005207-4). A combined herbal preparation of dry ivy leaf extract, decoction of thyme and aniseed, and mucilage of marshmallow root was tested for its efficacy and tolerability in open clinical trial and this preparation alleviated cough in consequence of common cold, bronchitis or respiratory tract diseases with formation of mucus.¹⁷³ Extract of *Serenoa repens* was analysed versus placebo in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (EudraCT Number: 2014-000222-38) and it was found effective in mitigating inflammatory biomarkers in these patients.¹⁷⁴ Polyherbal formulations of neem and other plants in the form of cream or tablet have been tested for their anti-human papilloma virus (HPV) potential in women infected with HPV type 16.¹⁷⁵

Neem leaf extract in herbal mouth rinse has been assessed for its effectiveness in controlling radiation induced mucositis in oral cancer patients (CTRI.2014/11/005163; NCT01898091). A randomised placebo-controlled clinical trial revealed alleviation of symptoms associated with osteoarthritis of the hip and knee with the use of an extract of *Artemisia annua* (ACTRN12614000259640).¹⁷⁶ Although, these studies have met with mixed results, however, positive results obtained in these trials certainly pave a way ahead for plant based medicine to be incorporated with conventional medicine.

4. Surmounting the challenges faced by botanicals

4.1. Improving procedures and guidelines

Although, not strictly followed by all countries, protocols for safety and toxicity testing have been devised by several agencies including Union of Pure and Applied Chemistry,¹⁷⁷ European Medicines Agency (EMA),¹⁷⁸ and the European Food Safety Authority.¹⁷⁹ Considering the complexity of herbal medicines viz a viz their content and action, organisations like WHO, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine, US Agency for Health Care Policy and Research, European Pharmacopoeia Commission, Department of Ayurveda, Yoga, Unani, Siddha, Homeopathy (India) are revising procedures and developing new protocols to standardise phytotherapy. Attempts are being made to resolve issues that occur due to nomenclature problems. Kew's Medicinal Plant Names Services has developed a freely accessible global resource that provides information about plant and plant products relevant to policy making and health regulation, traditional medicine, functional foods and pharmacological research. This database provides information of medicinally relevant plants pertaining to their frequently used vernacular, trade and pharmaceutical names.¹⁸⁰ The Uppsala Monitoring Centre (UMC) in collaboration with the Royal Botanic Gardens has established an effective system for standardisation and cross-referencing of herbal names in order to enable international reporting of ADRs due to herbal drugs. UMC has also been involved in developing the WHO herbal dictionary which serves as an international reference source of herbal products. This dictionary allows identification of herbal products, their bioactive constituents, possible therapeutic uses, coding and analysis of drug safety data during pre and post marketing. Herbal monographs have been published by American Herbal Pharmacopoeia, WHO, United States Pharmacopoeia, European Pharmacopoeia, EMA, Indian Pharmacopoeia etc.

Emphasis is being laid to improve the quality of ADR reporting and specialised centres have been set up worldwide for assistance in herbal pharmacovigilance. In USA, since herbal products are sold as dietary supplements and not as drugs therefore they are spared from pharmacovigilance obligations. However, health care practitioners and consumers are being made aware of the benefits of ADR reporting and are being guided to report ADR events to the FDA MedWatch Scheme. In UK, Medicines and Healthcare Products Regulatory Agency has a system for reporting of ADRs. In the EU,

when any herbal product is classified as a medicine then the manufacturers have pharmacovigilance obligations listed under European directives and other national regulations. This includes informing the regulatory agencies of any untoward or unexpected effects.⁹⁶ In UK, the Chinese Medicine Advisory Service with the help of Royal Botanic Gardens Kew helps with the enquiries on adverse effects and the identification of the Chinese medicinal herb suspected to be causing the effect. In Hong Kong toxicology centres in hospitals take up multidisciplinary investigations related to herbal toxicity. WHO Collaborating Centre for monitoring drug safety (UMC) collects ADR reports from over 100 countries and collates them with the purpose of addressing nomenclature issues and possibly co-relating the ADR with the correct herb.¹⁸¹ The database maintained by the UMC also provides useful information on the pharmacokinetic and pharmacodynamic drug interactions.¹⁸² Regulatory agencies around the world have started making efforts to facilitate the harmonization of regulatory requirements.⁶⁸ The Association of Southeast Asian Nations (ASEAN) consists of ten member countries each with its varying backgrounds of traditional medicine. ASEAN has formed a harmonized regulatory framework for traditional and HMPs. This framework includes common agreements on additives, excipients, pesticide residue levels, labelling requirements etc.^{183,184}

4.2. Improving trial design and ensuring quality control

High quality scientific research intended for the safety and efficacy of HMPs is essential to instil confidence in practitioners of conventional medicine to adopt HMPs as alternatives for disease management. However, the high costs of research and development deter the manufacturers of herbal products from delving into this space. This deterrent can be surmounted by applying for a patent. Although, it is difficult to claim exclusive rights for growing herbs, spices, plants etc, however, this should not dissuade the manufactures from venturing into HMP research since patents can also be granted on the basis of novelty related to processing and formulating HMP, unique compositions and their intended use for a medical purpose.^{185–188} Patents have been granted for HMP based on novel poly herb compositions, dosage forms, establishment of new processes for isolation and standardization of active compounds.¹⁸⁶

Clinical trials carried out with placebos and/or reference medicines before marketing are very important in revealing potential adverse effects emanating from the use of a particular drug. However, these clinical trials are of a short duration and are incapable of providing information on problems (such as long term effects) that are not comprehensively addressed by clinical trial protocols. Therefore, to evaluate long term toxicity and safety potentials, long-term carcinogenicity tests, reproductive and teratogenicity potentials should be assessed. Moreover, many a times some rare and severe adverse effects resulting due to interactions with drugs and nutrients come to the forefront in subgroups of people not included in the randomized control trials (RCTs). Such events are likely to be detected only when the drug is in use by a larger section of the population. Post-marketing surveillance of HMPs could help in keeping track of such effects.⁵²

The researchers should resort to high quality clinical trials and adhere to good reporting. Considering the shortfalls in trial reporting, the CONSORT statement has been amended with an aim to improve research and reporting quality with botanicals. Recommendations have been made with context to complete and transparent reporting of trials.^{57,189,190} Due emphasis has been laid on the standardization of the HMP because many a times the amount of the active ingredient is not known and is known to vary between preparations.^{60,191,192} The researchers must fully describe the preparation of placebos used in HMP trials so as to enable other researchers in carrying out related placebo-controlled trials in order to control bias that may occur due to the peculiar organoleptic properties of clinical preparations and their respective placebos.¹⁹³ Caution must be practiced while designing clinical trials, laying stress on the internal and external validity of the tests used thereof. It is essential that the output of the results in the control conditions of the study find relevance in being used outside the experimental settings of the study (refers to the harmony between internal and external validity). This implies that the study findings give meaningful insights when applied in the 'real' situations.^{194,195} Further, for the results to be externally valid it must be ensured that the disease criteria for inclusion and exclusion should be relevant with the diagnostic procedures currently used.⁴⁸ Cluster RCTs may be designed in order to establish the variabilities of the practitioners while evaluating the efficacy of the HMPs.⁴⁸

It is known that ayurveda recommends personalized treatment on the basis of an individual's 'prakriti' and 'tridoshas'. 'Ayurgenomics' is an upcoming field of study which serves to bridge the gaps between genomic influences and Ayurvedic principles. It is an integration of principles of genomics with that of ayurveda and is aimed at studying inter-individual differences to disease development and therapeutics by inter-relating their psychosomatic constitution and their genetic makeup.^{196,197} Such integration of disciplines could help in designing trials with ayurvedic remedies.

As defined by the EMA, chemical markers are chemically defined constituents or group of constituents intended for the control of quality. Chemical markers are employed in the standardization process to ensure that all batches contain a defined amount of the active ingredient. The choice of the chemical marker/s is essential to the quality of the herbal product. These could be of two types: active markers and analytical markers. Active markers possess therapeutic potentials while the latter ones are solely used for analytical purposes and have no therapeutic value.¹⁹⁸ It must be understood that using a single active marker may not give a true representation of the synergistic effects of the various bioactive constituents present in the HMP.^{199,200} And similarly, using an inappropriate analytical marker may not appropriately give the indication of the potency or quality of HMP. Using a non-specific analytical marker (e.g. quercetin, oleanolic acid etc) will fail to recognize an adulterated HMP because of the widespread presence of the marker being used.^{201,202} Using a chemical marker alone for standardization and quality control of HMP has its disadvantages. Therefore, other methods must be used in tandem.

Chromatographic fingerprinting is an analytical method that employs high performance liquid chromatography, thin layer chromatography (TLC), and gas chromatography techniques.^{193,199,203} These techniques give a fingerprint which is unique to a HMP. This fingerprint comprises of a set of peaks which are characteristic of the herbal ingredients present. Thus, a unique fingerprint generated helps in qualitative and quantitative analysis. Principal component analysis can be used to compare fingerprint patterns to detect adulteration.^{203,204} For polyherbal preparations^{204,205} and preparations with closely related species (e.g. *Heracleum sphondylium* and *Heracleum sibiricum*),²⁰⁶ a single chromatographic analysis may be insufficient. To resolve the details of polyherbal formulations 2D-TLC,^{206,207} multiple chromatographic fingerprinting^{143,154,193,204} and metabolite fingerprinting are advisable.^{205,208–210}

The regulators should perform targeted chemical analysis on every batch of HMPs to check for adulterants. To evade detection, manufacturers have started adding chemical drugs or their modified analogues to the capsule shells.^{211–213} In order to detect adulteration of this sort, reference spectra of these shells and analogues should be recorded with the aid of analytical techniques like liquid chromatography–mass spectrometry (LC–MS),^{214,215} nuclear magnetic resonance spectroscopy,^{215,216} infra-red spectroscopy.²¹⁶ Considering the transnational movement of HMPs, it is required that the regulators and manufacturers involve in information sharing relating to detection of adulterants. Consumers can play their part by buying HMPs from reputable and trust worthy sources. In order to grapple with the unethical manufacturers and miscreants the consumers should be particular about details such as manufacturing and expiry dates, batch numbers, names and addresses of HMP manufactures. Having clear product categorization will enable sufficient safety checks. It is known that regulated HMPs are equipped with better product information details enabling the customers to make more informed choices, thus promoting the safe use of HMPs. With the growing popularity of HMPs and its worldwide acceptance, it is required that authorities harmonize their regulatory requirements so as to bring about transparency and convenience for manufacturers and consumers.

For the standardization of herbal drugs, tests can be applied based on several established standards including pharmacopeial standards, marker based phytochemical assays, process control standards, storage standards, polyherbal reference standards, chemi-informatics approaches based structural standards²¹⁷ which include a range of physical, chemical and biological tests. Correct identification of plant involves ascertaining the correctness of the plant chosen based on its taxonomical classification, its morphological features etc. The part of plant to be used should be confirmed by matching its characteristic botanical features. Also, assessing the level of exposure of the plant part to the environment helps in deciding the levels of adulterants/contaminants.²¹⁸ Removal of foreign organic matter involves removing other organic matter (like weeds etc) that may sometimes come along with the raw plant material. This is essential to avoid interference during the standardization. Estimation of ash values (total ash, sulphated ash, water soluble ash, acid insoluble ash) should be done by performing thermo-gravimetric

analysis, differential thermal analysis and differential scanning calorimetry.^{219–221} Moisture content must be determined precisely to assess the actual weight of the drug. Low moisture content increases the stability of the drug.²¹⁷ Extractive values which are indicative of the extractable chemical constituents of the crude drug (under different solvent conditions) must be evaluated as they are important in dose calculation. The qualitative analysis of the crude drug involves screening of the various phytochemical constituents like flavonoids, alkaloids, phenolics, carbohydrates etc which are of pharmacological significance.²²² LC–MS has previously been employed to standardize an aqueous extract of the mixture of twenty herbs. This method provided twenty chemical compounds to be used as reference markers.^{223,224} Quantitative analysis should be performed for the levels of different elements, minerals, heavy metals etc. Microbial assays should be carried out to establish the presence of mycotoxins, harmful fungi, bacteria and other microorganisms. Toxicology studies should be performed in relevant animal models to generate LD50 values and other relevant parameters which are required for subsequent studies by the drug regulators. These give information about potentially toxic elements, pesticide levels etc.^{203,225} In order to ensure process control standards, batch analysis should be done by performing intermediate testing using appropriate methods. Tests should be performed to check for any process induced toxicity and impurity. Storage standards should also be applied by determining storage standard markers for raw material, stable intermediates from fractions, processed material, and finished product. The shelf life of the finished product in various conditions of temperature, humidity should be also determined. Packaging material and labeling standards should also be checked.²¹⁷ Polyherbal reference standards are established by comparing the reference standard of a single constituent in exclusion and its profile in polyherbal formulations. Chemi-informatic approaches include activity descriptors and its correlation modeling with poly-constituent profile based indicators.

For the safe and effective use of quality botanicals, it is utmost necessary that strict pre-market and post-market evaluation is carried out. The dealers of the herbal products (manufacturers, packagers, distributors, sellers etc) should be made to satisfy specific legal requirements such as GMP, ADR etc associated with the use of their HMPs. It is beyond doubt that quality of starting material affects HMP quality. Therefore, good agricultural practices (GAP) should be followed along with GMP. In many countries, the manufacturers have to conform to GMP before a license can be granted for production of HMP, although GAP is not legally mandatory for cultivators and manufacturers.⁶⁸ To ensure good quality of HMPs compliance to both GMP and GAP should be made mandatory. Medicinal plant cultivation through contract farming would ensure the quality of the produce and minimise the variability in plant preparations and maintain good quality products.

Through well designed educational and awareness programmes people need to be informed about the possible good and adverse effects of NHPs. Health care practitioners/clinicians also need to be provided in depth knowledge about medicinal plants/herbs and their putative health effects. A better interaction between the clinicians and patients with efficient exchange of information would help

reinstate the efforts that are being put to establish the database of plant based medicine.

5. Conclusion

The growing popularity of over-the counter available health products, dietary supplements, nutraceuticals obtained from plants has highlighted certain issues which need to be addressed at priority. These polychemical mixtures containing many pharmacologically active compounds need a thorough scientific and clinical evaluation in order to bring them to mainstream therapeutics. The perception of natural being safe can only be realised if these products are manufactured under strict regulatory controls and assessed for their efficacy. Through implementation of good agricultural, manufacturing and supply practices it would be possible to improve the quality of herbal medicines making them of a reproducible quality. A collaborative effort of the researchers, clinicians and patients is required to successfully establish herbal medicine in health promotion and disease management. Although evidences exist for the beneficial effects of plants against diseases and in health promotion, however the use of plant derived preparations can only be realised after the affirmation of their safety and efficacy. With such reassurances it could be possible to replace some synthetic drugs with herbal medicines or use them in combination with other drugs; thus enabling their integration into contemporary medicine.

Conflict of interest

Authors declare no conflicts of interest.

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